

# Current developments of potentially significant Triazole derivatives

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## General Note



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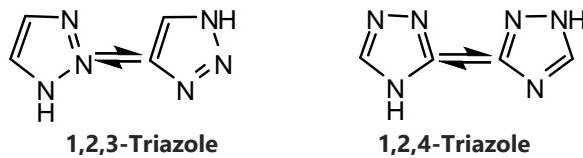
## ABSTRACT

Heterocyclic compounds analogues have attracted strong interest due to their useful pharmacological properties. Triazole is a five membered heterocyclic system consisting of two carbon atoms and three nitrogen atoms shows wide range of biological activities. The small triazole nucleus is present in various compounds that possess various types of biological activities, such as, anti-microbial, antibacterial, antifungal, antiviral, anti-malarial, anti-tumor, anthelmintic, antileishmanial, anticonvulsant, antidepressant, antihypertensive, analgesic, anti-inflammatory and hypoglycemic properties. Scientists develop a lot of new compounds related to this moiety and screened them for their different pharmacological activities to get a molecule which have good pharmacological activity and lesser side effect. This reviews attempted the various developments in biological activities of triazole derivatives.

**Keywords:** Triazoles, heterocyclic, anti-microbial, anti-malarial, anticancer, biological activities.

## 1. INTRODUCTION

1,2,4-Triazole is one of a pair of isomeric chemical compounds. Triazoles are heterocyclic compounds featuring five member ring of two carbon atoms and three nitrogen atoms as part of the aromatic five-member ring. Triazole refers either one of a pair of isomeric chemical compounds with molecular formula  $C_2H_3N_3$ . 3-Amino-1,2,4-Triazole is a white solid, soluble in water with a melting point 157-159°C with density 1.138g/mol and a competitive inhibitor of the production of HIS3 gene, imidazole glycerolphosphate dehydratase. It is an enzyme catalyzing the sixth step of the Histidine production and is also a non selective systemic triazole herbicide used on non food crop land to control annual grasses and broad leaf and aquatic weeds. 4-Amino-1,2,4-Triazole is a needle like white crystal with a melting point 84-86°C. It is hygroscopic in nature, soluble in water and ethanol [1]. The chemistry of heterocyclic compound continuous to be an explore field in the organic or medicinal chemistry. The importance of triazole derivatives lies in the field that these have occupied a unique position in heterocyclic chemistry, due to its various biological activities [2]. Triazole refers to either one pair of isomeric chemical compound having membered ring of two carbon atom and three nitrogen atoms. The two isomers are 1,2,3-triazole and 1,2,4-triazole (Figure 1).

**Fig 1.** Structure of triazoles

The derivatization of triazole ring is based on the phenomenon of bioisosterism in which replacement of oxygen of oxadiazole nucleus with nitrogen triazole analogue. Out of the two triazoles, 1,2,4-triazole has wide variety of activity [3]. Triazole moiety is an important and frequent insecticide, agrochemical structure feature of many biological active compounds such as cytochrome p450 enzyme inhibitors and peptide analog inhibitor. Like the azoles, triazoles are used in many antifungal drugs and fungicides, but the triazole-based drugs are more selective for fungi than mammalian cells than the azole-based antifungal compounds. The azoles are the class of antifungal agent either an imidazole or a triazole group joined to an asymmetric carbon atom as their functional pharmacophore treatment for fungal infections like Ketoconazole, Fluconazole, Voriconazole and Ptraconazole. The 1,2,4-triazole are also used as analgesic antiasthmatic, antibacterial, anticholinergic, antidressant agents etc. They are aromatic ring compounds similar to the azole, pyrazole and imidazole but with an additional nitrogen atom in the ring structure [4].

## 2. BIOLOGICAL ACTIVITIES OF TRIAZOLE DERIVATIVES

The 1,2,4-triazole nucleus has been incorporated into a wide variety of therapeutically important agents. Ribavirin (antiviral) [Crotty, et al., 2000], Rizatriptan (antimigraine) [5], Vorozole, Letrozole and Anastrozole (antitumor) [6] are some examples of drugs containing 1,2,4-triazole moiety. Posaconazole, Fluconazole and Itraconazole [7,8] are efficient antifungal drugs used in current treatment. A number of biological activity such as antibacterial antifungal [9,10], anti inflammatory, analgesic [11] anticonvulsant [12], anticancer [13,14] antitumor [15,16], antiviral [17], antileishmanial [18], potassium channel activators [19], antiplatelet [20] and antioxidant [21] have been associated with N-substituted triazole attached with different heterocyclic nuclei. For the design of new bioactive agents, the development of hybrid molecules through the combination of different pharmacophores in the same structure may lead to compounds having more efficiency in biological activity. The systematic structural modifications of the amide-1,2,3-triazole leads to develop of bioisosteric relationship in the molecule [22]. The interesting biological activities were associated with triazole derivatives. The triazole derivatives associated with large number of biological activities is presented below.

### Antifungal activity

A series of compound 3-[4-(substituted phenyl)-5-thioxo-4,5-dihydro-1H-1,2,4-triazole-3-yl-methoxy]-phenyl]-2-phenyl-3H-quinazoline-4-one (**1a-c**) screened for antifungal activity. The compound (**1c**) 3-{4-[nitrophenyl]}-5-thioxo-4,5-dihydro-1H-[1,2,4]triazole-3-yl-methoxy]-phenyl]-2-phenyl-3H-quinolin-4-one exhibit good activity against *Aspergillus niger* [23]. A series of compound 7-(3-(1H-1,2,3-triazole-1-yl)propoxy)-4methyl-2H-chromen-2-one (**2a-c**) and screened for *in-vitro* antifungal activity against strain of *Candida albicans*. All compounds except compound (**2b**) showed moderate antifungal activity while compound (**2c**) 7-(2-(1H-1,2,3-triazole-1-yl)-4-(4-nitrostyryl))2H chromen-2-one which is nitro substituted at Para-position showed antifungal activity as comparable to Ketoconazole [4]. A series 3-(un)substituted-7-aryl-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazoles compounds and its derivatives which is screened for antimicrobial and antifungal activities. 7-(4-Chlorophenyl)-5H-6,7-dihydroimidazo[2,1-c][1,2,4]triazole-3-thiol (**3**) showed the superior antifungal activity as compared to Miconazole [14]. A new series of 1-(2-hydroxy-2-phenyl-ethyl)-3-thiophen-2-ylmethyl-4-[arylidene-amino]-4,5-dihydro-1H-[1,2,4]triazole-5-ones and 1-(2-hydroxy-2-phenyl ethyl)-3-thiophen-2-ylmethyl-4-[aryl-amino]4,5-dihydro-1H-[1,2,4]triazole-5-ones were screened for their antifungal activity. The derivatives of compound (**4**) exhibited significant antifungal activity [24]. The 3,5-Diaryl-4H-1,2,4-triazole derivatives were tested for their fungicidal activity against *P. oryzae*, *B. cinerea*, *A. niger*, *C. albicans* and *T. rubrum*. Compounds (**5**) showed significant and comparable activity with Griseofulvin against *P. oryzae*, *B. cinerea*, *A. niger*, *C. albicans* and *T. rubrum* at 1000 ppm concentration [25]. The twenty eight derivative of 4-amino-5-substituted aryl-3-mercapto-1,2,4-triazoles have been tested in vitro against *Rhizoctonia solani*, *Sclerotium rolfsii*, *Fusarium oxysporum*, *Pythium aphanidermatum*, *Puccinia recondite* and *Bipolaris sorokiniana*. Compound (**6**) exhibit highest activity against *P. recondite* ( $ED_{50}=12$  mg/ml) and the compound (**7**) exhibit highest activity against *Bipolaris sorokiniana* ( $ED_{50}=27$  mg/ml) [26]. The 9-substituted-3-aryl-5H,13aH-quinolino[3,2-f][1,2,4]triazolo[4,3-b][1,2,4]triazepines were

screened for antifungal activity against *Aspergillus flavus*, *A. niger*, *Rhizopus* species and *Penecillium notatum* species against two concentration 500 $\mu$ g/ml and 1000 $\mu$ g/ml. the compound (**8,9,10,11**) showed excellent antifungal activity against *A. niger* and *P. notatum* at 500 $\mu$ g as well as and 1000 $\mu$ g. Some azoles exert antifungal activity through inhibition of CYP51 by a mechanism in which the heterocyclic nitrogen (N-3 of imidazole or N-4 of 1,2,4-tiazole) binds to the sixth coordination of heme iron atom of the porphyrin in the substrate binding site of the enzyme [27].

### Antibacterial activity

The mannich bases of triazole were assayed *in vitro* for their antimicrobial activity against *Acinetobacter baumanii*, *Citrobacter freundii*, *Pseudomonas aeruginosa*, *Enterococcus faecalis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Bacillus subtilis* and result showed that (4-X-phenylsulfonyl)phenyl moiety in all these derivatives was not a very important factor for their antibacterial activity, since both compounds with X=H, or X =halogen showed similar activity. The derivative compound (**12**) exhibited promising antibacterial activities against *A. baumanii*, *Bacillus subtilis* [28]. The 1,2,3-triazole substituted 1,3,4-oxadiazoles derivative were evaluated for antimicrobial activity. The triazole moiety reacts with different aromatic acids which lead to compounds more active and showed good antibacterial activity against *S. aureus* and *Escherichia coli* [29]. A series of *N*-[3,5-dialkyl-4*H*-1,2,4-triazol-4-yl] acetamides, 4-arylideneamino-3,5-dialkyl-1,2,4-triazoles, 4-alkylamino-3,5-dialkyl-1,2,4-triazoles were exhibited as a potent antifungal agents. The best activity was observed against *C. albicans* by compound (**13**) [30]. A series of Schiff and mannich bases of triazole containing pyrazole skeleton evaluated as antimicrobial agent against *S. aureus*, *B. subtilis*, *E. coli*, *P. aeruginosa* and *C. albicans*. Compound (**14**) showed good minimum inhibitory concentration (MIC) at 3 mg/ml concentration against all the tested bacterial strains [31]. Schiff's bases as *N*-[1-aryl-methylene]-1-[8-(trifluoromethyl)quinolin-4-yl]-5-methyl-1*H*-1,2,3-triazole-4-carbohydrazide and 1-Aryl-4-{1-[8-(trifluoromethyl)quinolin-4-yl]-5-methyl-1*H*-1,2,3-triazol-4-yl}prop-2-en-1-one containing triazole and quinoline moiety [32]. These compounds were screened for their antimicrobial activities against *E. coli*, *S. aureus*, *P. aeruginosa*, *B. subtilis*, *Klebsiella pneumonia*, *Aspergillus flavus*, *A. fumigatus*, *C. albicans*, *Penicillium marneffei*, *Trichophyton mentagrophytes*. The compound (**15**) was most active and exhibited the maximum antimicrobial activity against all bacterial and fungal strains almost equivalent to that of the standard drug [33]. The 5-[(1*H*-Indol-3-yl)methyl]-4-arylideneamino-3-mercaptop-1,2,4-triazoles and 3-[(1*H*-Indol-3-yl)methyl]-6-aryl-7*H*-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazines exhibited antimicrobial activities against *Micrococcus luteus*, *Bacillus cereus*, *Proteus vulgaris*, *Salmonella typhimurium*, *S. aureus*, *E. coli*, *C. albicans* and *Candida glabrata*. Among these series compound [**16**] including the methyl on phenyl showed significant antifungal and antibacterial activity. A series of 5-phenyl, 4-(substituted) amino, 3-mercaptop 1,2,4-triazoles (**17**) which showed potent anti-bacterial activity [3]. A series 3-(un)substituted-7-aryl-5*H*-6,7-dihydroimidazo[2,1-c][1,2,4]triazole compound (**18**) are synthesized. Their anti-bacterial activity and its derivatives such as 3(2,4-Dichloro phenoxy methyl)-7(3,4dichlorophenyl-5*H*-6,dihydroimidazo[2,1c][1,2,4]triazoles showed superior *in vitro* anti-bacterial activity then compared to Ampicillin and Chloramphenicol [34]. A series of compound 5-[2-(substituted sulfamoyl)-4,5-dimethoxybenzyl]-4aryl-s-triazole-3-thiones (**19a-c**) were screened for anti-bacterial activity and its series derivative compound showed inhibitory effect at 100.0  $\mu$ g/ml against *E. coli*, which has the same MIC as antibiotic Streptomycin but much better than Chloramphenicol on MIC at 250.0  $\mu$ g/ml [35]. Glucosidation of some 4-amino- and 4-arylideneamino-5-(pyridin-3-yl)-2,4-dihydro-1[2,4]-triazole-3-thiones (**20**) with 2,3,4,6-tetra-O-acetyl-a-D-glucopyranosyl bromide gave the corresponding N- and S-b-D-glucosides. Deamination as well as deacetylation of some selected nucleosides have been achieved. Antimicrobial screening of some selected compounds showed their activity against *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, *C. albicans*, *S. aureus*, *P. aeruginosa*, *B. subtilis*, and *E. coli* [36]. Ethyl 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptopacetate (**21**), 5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptopacetic acid hydrazide (**22**) and a series of *N*-alkylidene/arylidene-5-(2-furyl)-4-ethyl-1,2,4-triazole-3-mercaptopacetic acid hydrazides (**23**) were evaluated for *in vitro* antibacterial activity against *S. aureus*, *S. epidermidis*, *Klebsiella pneumoniae*, *P. aeruginosa*, *E. coli*, *Shigella flexneri*, *S. typhi*, *Proteus mirabilis* and antifungal activity against *C. albicans*. The *in vitro* antitubercular (anti-TB) activity of the compounds against *Mycobacterium tuberculosis* H37Rv was evaluated. The highest inhibition observed was 61% at 6.25 $\mu$ g/ml [37].

### Antitubercular activity

Series of 3-benzylsulfanyl derivatives of 1,2,4-triazole (**24**) and 4-methyl-1,2,4-triazole were evaluated for *in vitro* anti-TB activity against *M. tuberculosis*, *M. avium*, and two strains of *M. kansasii*. The compounds exhibited only a moderate or slight anti-TB activity. The MICs fall into a range of 32->1000  $\mu$ mol/l. The most active substances bear two nitro groups or a thioamide group on the benzyl moiety. As regards the cytotoxicity effect, the evaluated compounds can be considered as moderately toxic [38]. A series of N-substituted-phenyl-4-difluoromethyl-1,2,3-triazoles were evaluated them for anti-TB activity against *M. tuberculosis* H37Rv strain.

Chlorine and methyl substituted derivative exhibited the 100% inhibition with MIC values of 2.5 $\mu$ g/mL. The carbaldehyde group seems to be important to the interaction with the target receptor. The fluorine atom produced negatively affect for the anti-TB activity. The result showed that the presence of the hydrogen bond acceptor subunit, the position in the aromatic ring, the planarity of triazole and phenyl rings in these compounds were important for exhibiting the anti-TB activity [39]. The 2-[4-(1H-[1,2,4]-triazol-1-yl)phenyl]-1-substituted-4,6-difluoro-1H-benzo[d]imidazole derivatives were evaluated them for anti-TB activity against *M. tuberculosis* H37Rv by microplate alamar Blue assay (MABA) and observed that the activity is increased with increase in electronegativity of molecule. Compound (25) exhibited good activity at 6.25mg concentration, while the activity is decreased when substituted with trifluoromethyl group due to high electronegativity [40].

### Antimalarial activity

A series of derivatives such as 3-[4-(4-substituted phenyl-5-thioxo-4,5-dihydro-1H-[1,2,4]-triazol3ylmethoxy)-phenyl]-2-phenyl-3H-quinazolin-4 ones (26) and screened for anti-malarial activity. Among these derivatives, compound (26b) 3- {4-[4-(4-fluoro-phenyl)-4H-[1,2,4]triazol-3-yl-methoxy]-phenyl}-2-phenyl-3H-quinazolin-4-one is most active against strains *Plasmodium falciparum* [23].

### Anti-inflammatory activity

A series of ethyl 5-(un)substituted benzamido-1H-1,2,4-triazole-3-acetate were screened them for anti-inflammatory activity by carageenan-induced rat paw edema test and ulcerogenic effect. Compound (27) showed higher anti-inflammatory activity than the 5-acylamino derivatives, In the acyl substituents derivatives, the order of the anti-inflammatory activity was 4-nitrobenzoyl > 4-bromobenzoyl > 4-chlorobenzoyl > 4-methoxybenzoyl > unsubstituted benzoyl. The molecular dockings as well as conformational alignment studies showed that derivative of compound [22,41] exhibited higher affinity for the COX-2 active site and hence increased anti-inflammatory activity will be increased. A series of 3-(methyl/ethylsulfonyl)-5-aryl-1,2,4-triazole (28) were screened them for their anti-inflammatory analgesic activity and results showed that compounds having an alkylsulfone derivative were greater active than those of alkylthio group. Chlorine substituted on phenyl ring showed better results as compared to bromine substitution. Compounds [29] and [30] having 2-chlorophenyl and 4-chlorophenyl exhibited the highest analgesic and anti-inflammatory activity, at 50 mg/kg dose level [42]. A series of 1acylthiosemicarbazides, 1,2,4-triazole-5(4H)-thiones, 1,3,4-thiadiazoles and hydrazones containing 5-methyl-2-benzoxazolinones were evaluated for anti-inflammatory and analgesic activity [26,43]. A series of [(4-Amino 5-Disubstituted-4-H-1,2,4-triazole-3-yl)thio] alkanoic acid derivatives were screened for anti-inflammatory activity. Among these derivatives compound (31) showed significant anti-inflammatory activity [44]. The 3-[1-(4-(2-methylpropyl)phenyl)ethyl]-1,2,4-triazole-5-thione (33) and its condensed derivatives 6-benzylidenethiazolo[3,2-b]-1,2,4-triazole-5(6H)-ones were evaluated as anti-inflammatory agent. In gastric ulceration studies these compounds were generally found to be safe at a 200 mg/kg dose level [45]. A series of derivatives of 4-Amino-3-Aryloxy alkyl, 5-Mercapto-1,2,4-Triazole were evaluated for anti-inflammatory activity. Compound (32) showed potent anti-inflammatory activity [46]. The different acylated 1,2,4-triazole-3-acetates (34) with the objective of discovering novel and potent anti-inflammatory agents. These compounds were evaluated for their anti-inflammatory activities as well as gastric ulcerogenic effects and acute toxicity [41]. A series of compound 5-[(Biphenyl-4-yloxy)methyl]-4-nsubstituents-3-mercaptop-(4H)-1,2,4-triazoles were screened for anti-inflammatory activity, out of these compounds, 5-[(Biphenyl-4-yloxy)methyl]-4-nbutyl-3-mercaptop-(4H)-1,2,4-triazole (35) showed potent anti-inflammatory activity [47].

### Analgesic activity

A series of 5-[(Biphenyl-4-yloxy)methyl]-4-n-substituents-3-mercaptop-(4H)-1,2,4-triazole and its derivatives such as 5-[(Biphenyl-4-yloxy)methyl]-4- fluorophenyl-3-mercaptop-(4H)-1,2,4triazole (36) were screened for the analgesic activity. Compound (12) was showed analgesic activity ranging from 16.9% to 72.8%, whereas the standard drug flurbiprofen showed 69.5% inhibition [47]. A series of 1,3,4-oxadiazole/thiadiazole and 1,2,4-triazole derivatives (37) of biphenyl-4-yloxy acetic acid were exhibited potential anti-inflammatory, analgesic and lower ulcerogenic potential activity. These compounds were possessing potent anti-inflammatory, analgesic, ulcerogenic and antioxidant activities. These compounds showed significant analgesic effect and at an equimolar oral doses relative to flurbiprofen were also found to be non-gastrotoxic in rats (81.81%) than the reference drug (79.54%), low ulcerogenic potential and protective effect on lipid peroxidation [48].

### Anti-cancer activity

A series of compounds, 4-amino-3-substituted-5-oxo-4,5-dihydro-[1,2,4] triazole-1-yl acetic acid 2,4-dichloro-benzylidene-hydrazide derivatives were screened for their anti-cancer activity. The compound (**38**) 4-amino-3-phenyl-5-oxo-4,5-dihydro-[1,2,4] triazole-1-yl acetic acid 2,4-dichloro-benzylidene-hydrazide showed a potent therapeutic activity for the treatment of breast cancer [49]. The cytotoxicity of the compounds indicated good safety associated with many of the triazole derivatives. However, the need for standardized method for cytotoxicity evaluation is required for better understanding of the compounds safety and the structure activity relationships. The derivatives of 4,5-substituted-1,2,4-triazole-thiones (**39**) and 2,5-substituted-1,3,4-thiadiazoles were evaluated for their cytotoxicity.

The compounds 4-ethyl-5-(4,5,6,7-tetra hydro-1-benzothien-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**40**), N-ethyl-5-(4,5,6,7-tetrahydro-1-benzothien-2-yl)-1,3,4-thia-diazol-2-amine (**41**), 4-amino-5-(4,5,6,7-tetra hydro-1-benzothien-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**42**) and 4-amino-5-(5-phenyl thien-2-yl)-2,4-dihydro-3H-1,2,4-triazole-3-thione (**43**) possessed high cytotoxicity in vitro against thymocytes. The tested compounds showed a general stimulation effect on B-cells' response [50].

### Anticonvulsant activity

The substituted N-(5-mercaptop-3-pyridyl-3-yl-4H-1,2,4-triazol-4-yl)-thiosemicarbazone were evaluated for anticonvulsant activity by Maximum Electroshock (MES) method and found that total recovery time and time for hind limb extension. The recovery for compound [**44**] was less than the standard (Phenytoin) [51]. Compound 4-(4-alkoxylphenyl)-3-ethyl-4H-1,2,4-triazoles from the condensation of Dimethoxy-N,N-dimethylmethanamine, propionohydrazide and p-aminophenol were evaluated by the MES test and their neurotoxicity was evaluated by the rotarod neurotoxicity test and result showed that chlorine substituted derivative had more anticonvulsant activity than the fluorine substituted derivative and the activity order is 2-Cl > 2,6-Cl<sub>2</sub> > 4-Cl > 3-Cl and lengthening of the alkyl chain at C-7 of the 4-alkyloxy derivatives appeared to have a direct impact on anticonvulsant activity but activity is decreased at length C-12. Compound [**45**] produced significant antagonism activity against seizures induced by Pentylenetetrazole (ScPTZ), 3-mercaptopropionic acid, thiosemicarbazide and Isoniazid, suggested that the compound might have effects on GABA-ergic neurotransmission and activate glutamate decarboxylase (GAD) or inhibit (GABA)- $\alpha$ -oxoglutarate aminotransferase (GABA-T) in the brain [52]. Some substituted diphenyl-1,2,4-triazole-3-ones were screened for anticonvulsant activity. These compounds were screened by MES, sc PTZ, sc strychnine, and sc picrotoxin induced seizure threshold tests. Neurotoxicity screening was done by Rotarod test to detect the motor deficit in mice. Behavioral depression was measured by evaluating the locomotor activity of the animal using actophotometer, CNS depression was studied by Porsolt's swim pool test. Results show that compound [**46**] exhibited anticonvulsant activity in all the four animal models of seizure [53]. A series of 3-{{[(substituted phenyl)methyl]thio}-4-alkyl/aryl-5-(4-aminophenyl)-4H-1,2,4-triazoles (**47**) and several related Schiff's bases, 3-{{[(substituted phenyl)-methyl]thio}-4-alkyl/aryl-5-{{[(substituted phenyl/5-nitro-2-furyl)methylene]amino}-phenyl}-4H-1,2,4-triazoles were evaluated for their anticonvulsant properties. All compounds were evaluated for their anticonvulsant activity by MES, subcutaneous (sc) PTZ and neurotoxicity (NT) screens. A number of triazole derivatives, exhibited protection after intraperitoneal administration at the dose of 100 and 300 mg/kg. Some compounds also showed marginal activity against *M. tuberculosis* H37 Rv [54]. A series of 4-(4-alkoxylphenyl)-3-ethyl-4H-1,2,4-triazole (**48**) derivatives were synthesized as open chain analogues of 7-alkoxyl-4,5-dihydro[1,2,4]triazolo[4,3-a]quinolines (**49**). Their anticonvulsant activities were evaluated by the MES test and their neurotoxicity was evaluated. MES test showed that 3-ethyl-4-(4-octyloxyphenyl)-4H-1,2,4-triazole (**50**) was found to be the most potent with ED<sub>50</sub> value of 8.3 mg/kg and protective index (PI = TD<sub>50</sub>/ED<sub>50</sub>) value of 5.5, but compound, **50**, exhibited better PI value of 9.3, which was much greater than PI value of the prototype drug phenytoin. The compound **3r** was tested in PTZ test, isoniazid test, thiosemicarbazide test, 3-mercaptopropionic acid and strychnine test [52].

### Anti-depressant activity

A series of triazole substituted compounds were screened for antidepressant activity. Out of the synthesized compounds (**51**) 2,4-Dihydro-3H-1,2,4-triazole-3-thiones showed potential antidepressant activity [55].

### Antioxidant activity

Some 4-benzyl-idenamino-4,5-dihydro1H-1,2,4-triazol-5-one derivatives (**52**) were investigated for their antioxidant activity [56]. Schiff base of varies hetero ring possess diverse type of biological activities. A Series of Schiff's bases of 3-substituted 1,2,4-triazol-5-thione from the ester of methyl paraben as antioxidant by determining the hydrogen peroxide, Ascorbic acid was used as a standard. All The compounds showed good antioxidant activity which may be due to the presence of -SH group in the 5th position

[57]. The bis-triazole derivatives, 5,5/-methylene bis (4-substituted phenyl/alkyl-4H-1,2,4-triazole-3-thiol) screened for their antioxidant by DPPH method and anti-inflammatory activities by carrageenin induced paw oedema method. One of the compound [53] was found to have potent antioxidant and anti-inflammatory activity [58].

### **Endothelin receptor antagonist**

A series of 4-Amino-5-furyl-2-yl-4H-1,2,4-triazole-3-thiol derivatives were assayed for their Endothelin (ET) receptor antagonists by using the cell culture solution of the rat heart ventricle muscle membranes. Compound [54] showed a new leading compound of ET receptor antagonist which exhibited high inhibition of 71.93% [59].

### **Glycosidase inhibition**

A set of 4-Phenyl-1-b-D-Glucopyranosyl-1,2,3-triazole and 4-Phenyl-1-b-D-galactopyranosyl-1,2,3-triazole by the reaction of b-azido-galactopyranoside tetraacetate and b-azidoglucopyranoside Tetraacetate glycosyl triazoles as a Glycosidase inhibition. Glycosidase inhibitors are useful anti-viral, anti-proliferative, and anti-diabetic agents and the inhibitory activity evaluated against three b-glycosidase-sweet almond glycosidase (SAG), *E. coli* galactosidase (ECG), and bovine liver galactosidase (BLG) and the activity of the enzymes was compared in the absence and presence of the triazoles. Neither triazole was a good inhibitor of SAG. The glucose triazole [55] is a better inhibitor of BLG [60].

### **Urease inhibition**

The 5-aryl-4-(1-phenylpropyl)-2H-1,2,4-triazole-3(4H)-thiones is a potent inhibitor of Jack bean urease. Compound [56] was found to be more potent than the standard, with the IC<sub>50</sub> values of 7.8±0.2 compared to standard thiourea with IC<sub>50</sub>= 1.0 ± 0.1μM [61].

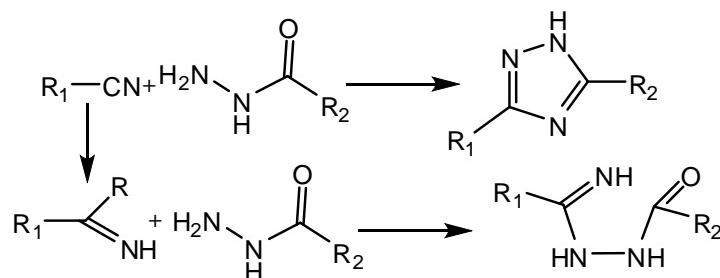
### **Plant growth activity**

A series of N-(5-((1H-1,2,4-triazol-1-yl)methyl)-4-tertbutylthiazol-2-yl)-4-carboxamide derivatives were evaluated as plant-growth regulatory activity by using cucumber cotyledon rhizogenesis method. The presence of fluorine atom at position 2,3,4 of phenyl ring are crucial for exhibited plant-growth regulatory activities and the substitution with chlorine atom at both 2-position and 4-position of benzene ring caused a decrease of the activity while the presence of a strong electron-withdrawing group such as nitro-group led to decrease in activity. Compound [57] having fluorine atom at 4th position connected to the phenyl ring produced excellent plant-growth regulatory activity [62].

## 3. METHODS OF SYNTHESIS

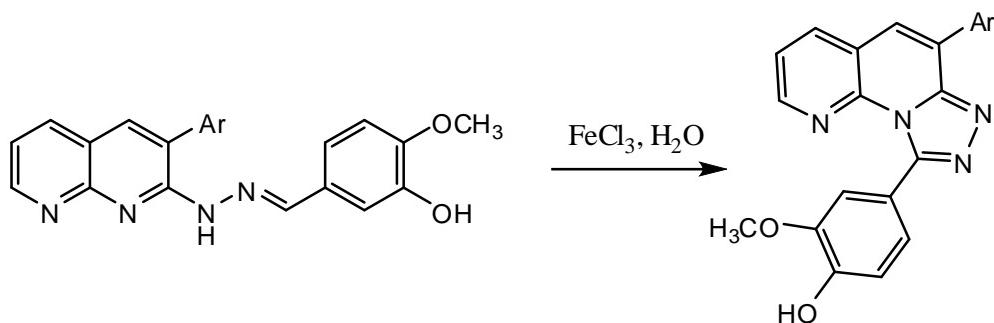
### **Base-catalyzed, direct synthesis of 3,5-disubstituted 1,2,4-triazoles**

A convenient and efficient one step, base-catalyzed synthesis of 3,5-disubstituted 1,2,4-triazoles by the condensation of a nitrile and a hydrazide is presented. A diverse range of functionality and heterocycles are tolerated under the reaction conditions developed, and the reactivity of the nitrile partner is relatively insensitive to electronic effects [63].

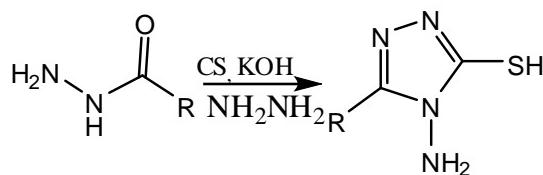


### **Solid phase synthesis of Triazole using FeCl<sub>3</sub> using Oxidative cyclization**

An efficient and mild method for the synthesis of 1,2,4-Triazole by the Oxidative cyclization in the solid state by grinding at room temperature has been described [64].



1,2,4-Triazole derivatives can also be prepared using Hydrazides, Carbon disulfide in presence of Base [65].



#### Microwave assisted synthesis of 1,2,4-Triazoles derivatives

The 1,2,4-Triazoles can be synthesized using catalytic amount of p-TsOH under Microwave irradiation rate enhancement and improvement in yields [66].

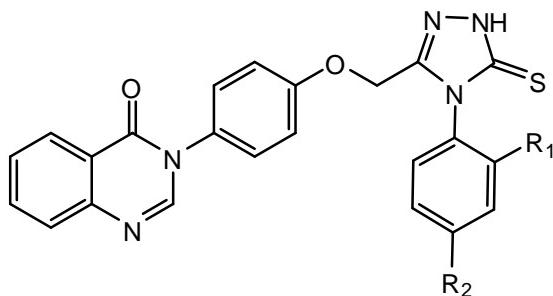
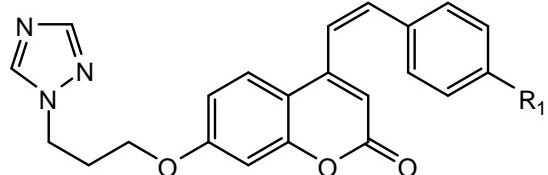
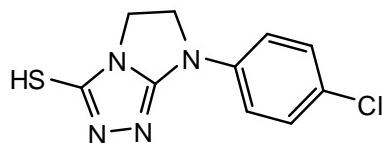
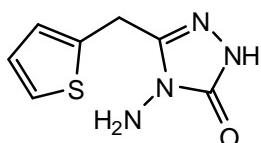
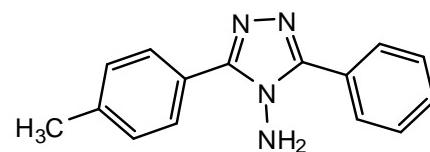
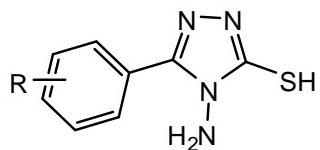
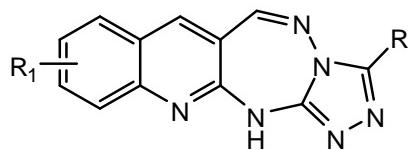
## 4. DISCUSSION

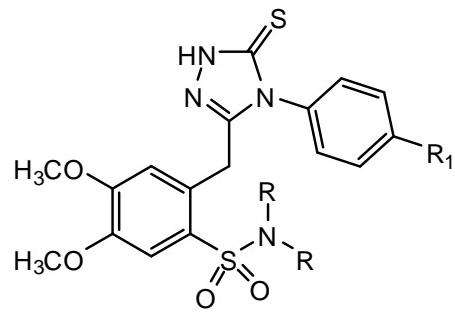
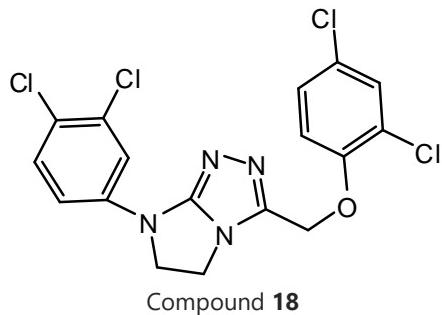
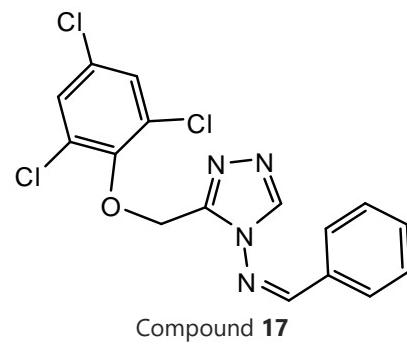
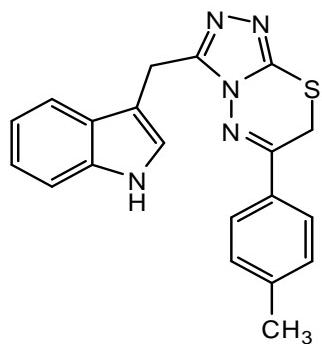
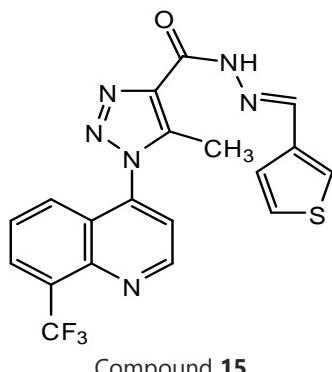
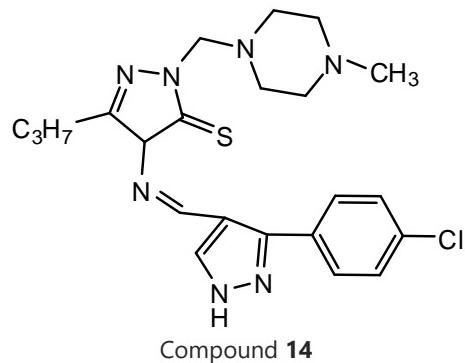
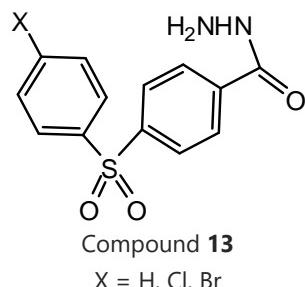
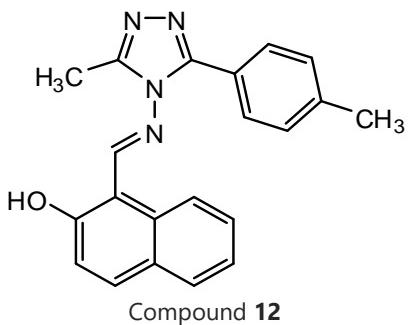
Medicinal chemistry is devoted to the discovery and development of new pharmacologically active agents for treating diseases. Heterocyclic molecules with increasingly specific pharmacological activities are clearly dominant in medicinal chemistry [67-71]. The objective of medicinal chemistry is design and the production of compounds that can be used as medicine for the prevention, treatment and cure of humans or animal diseases. It is concerned with the invention, discovery, design, identification of biologically active compounds, study of their metabolism, interpretation of their mode of action and structure activity relationship, the relationship between chemical structure and pharmacological activity for a series of derivatives have been synthesized as target structures and evaluated for their biological activities [72-75]. Modifications on triazole moiety displayed valuable biological activities. It will be interesting to observe that these modifications can be utilized as potent therapeutic agents in future.

## 5. CONCLUSION

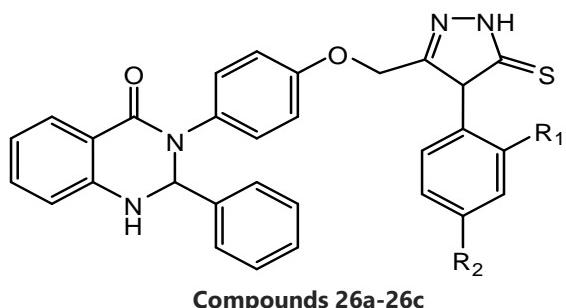
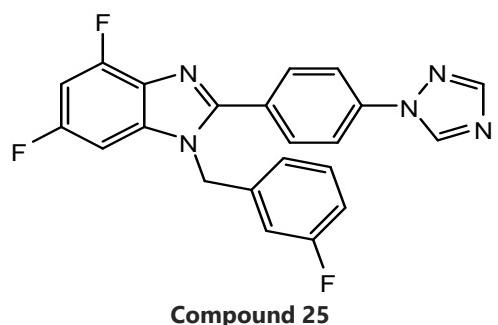
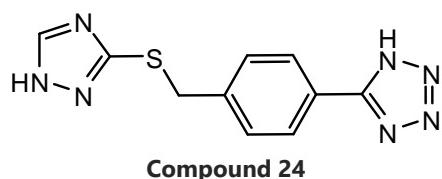
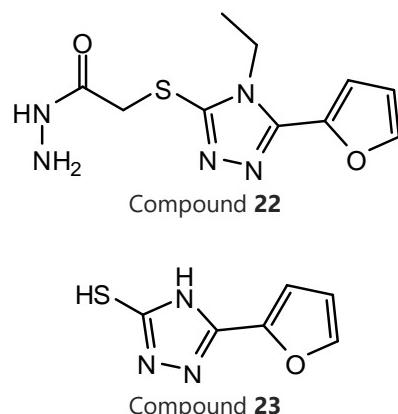
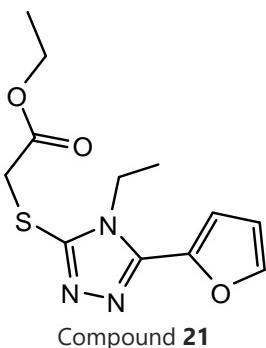
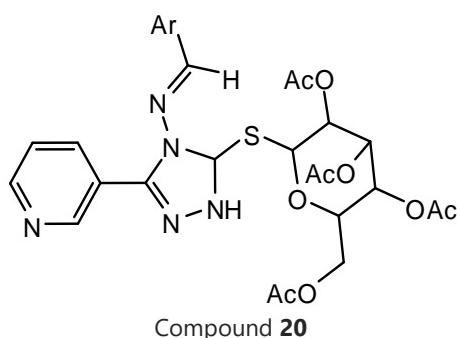
The plethora of research subscribed in this review indicates a wide spectrum of pharmacological activities exhibited by 1,2,4-triazole derivatives. The biological profiles of these new generations of 1,2,4-Triazoles would represent a fruitful matrix for further development of better medicinal agents. It can act as an important tool for medicinal chemists to develop newer compounds possessing Triazole moiety that could be better agents in terms of efficacy and safety. Triazole is a unique moiety that is associated with several biological activities. This article has highlighted different pharmacological activities of triazole compounds. This review has also presented comprehensive details of triazole analogues, potent compounds reported for particular pharmacological activity. More investigations must be carried out to evaluate more activities of triazole for many diseases whose treatment are difficult in the medical sciences. Thus the quest to explore many more modifications on triazole moiety needs to be continued for the use of mankind.

## APPENDIX

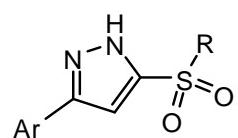
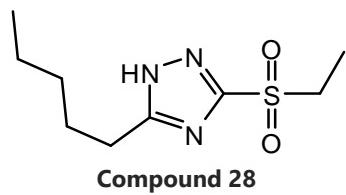
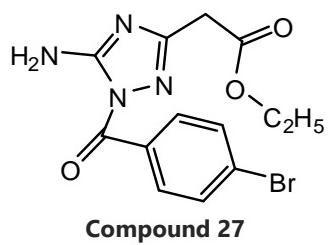
**Compounds 1a-1c****1a**  $R_1=H$ ,  $R_2=H$ ; **1b**  $R_1=H$ ,  $R_2=F$ ; **1c**  $R_1=H$ ,  $R_2=NO_2$ **Compound 2a-2b****2a**  $R_1= H$ ; **2b**  $R_1=NO_2$ **Compound 3****Compound 4****Compound 5****Compound 6 and 7** $R=2\text{-Cl}, 5\text{-NO}_2$ ; **7**  $R= 4\text{-CHO}$ **8**  $R= C_6H_5$ ,  $R_1=H$ ; **9**  $R= 4(\text{NO}_2)C_6H_4$ ,  $R_1=H$ ; **10**  $R= 2\text{-Cl } C_6H_4$ ,  $R_1=3\text{CH}_3$ ; **11**  $R=$  $4\text{-NO}_2C_6H_4$ ,  $R_1=3\text{CH}_3$ ;



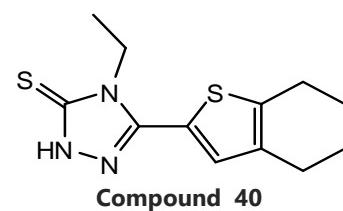
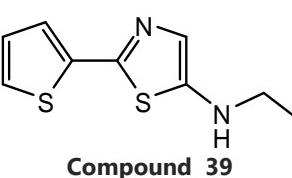
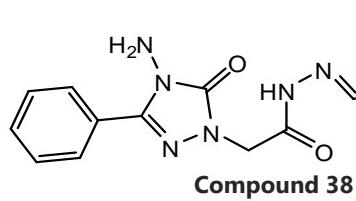
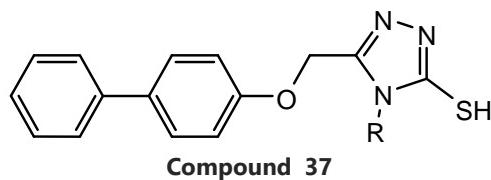
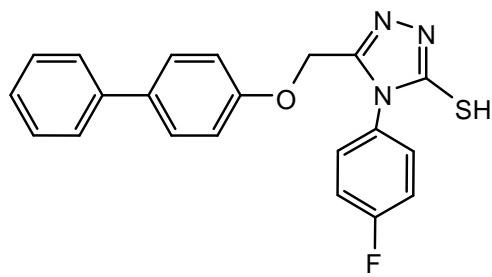
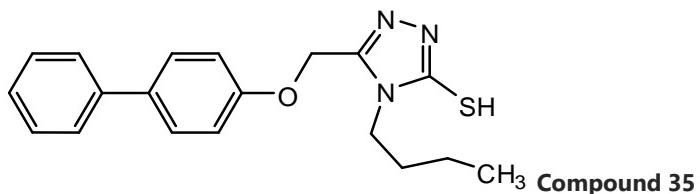
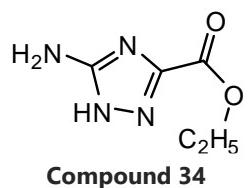
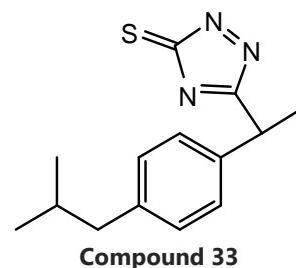
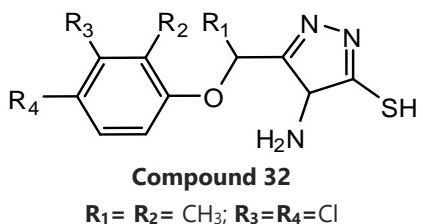
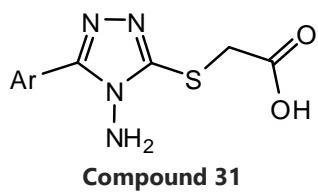
**19a** R=CH<sub>3</sub> R<sub>1</sub>=H; **19b** R=CH<sub>3</sub> R<sub>1</sub>=Cl; **19c** R=C<sub>2</sub>H<sub>5</sub> R<sub>1</sub>=H

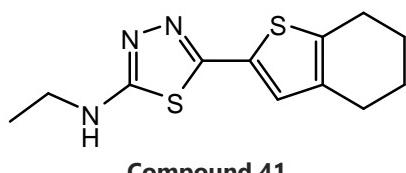


**26a** R<sub>1</sub>= H R<sub>2</sub>=H  
**26b** R<sub>1</sub>= H R<sub>2</sub>=F  
**26c** R<sub>1</sub>= H R<sub>2</sub>=NO<sub>2</sub>  
**26d** R<sub>1</sub>=F R<sub>2</sub>=F

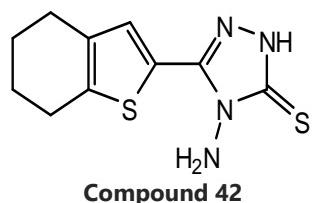


**29** Ar= 2-ClC<sub>6</sub>H<sub>4</sub>, R=C<sub>2</sub>H<sub>5</sub>  
**30** Ar=4-ClC<sub>6</sub>H<sub>4</sub>, R=C<sub>2</sub>H<sub>5</sub>

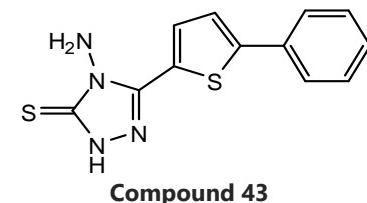




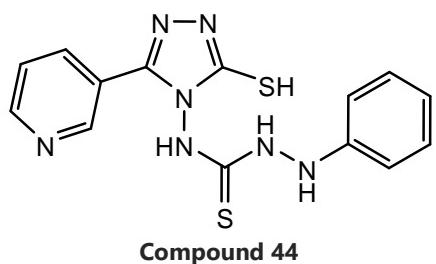
## Compound 41



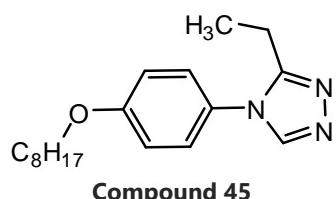
Compound 42



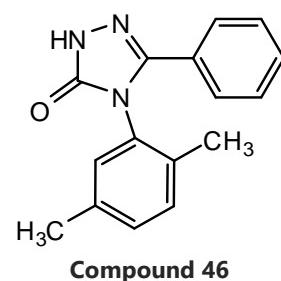
Compound 43



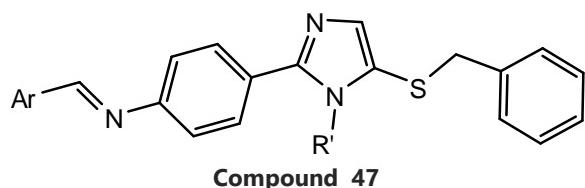
## Compound 44



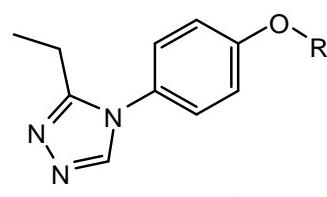
## Compound 45



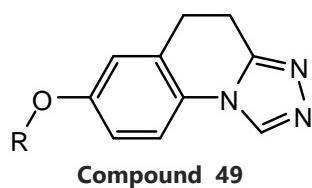
## Compound 46



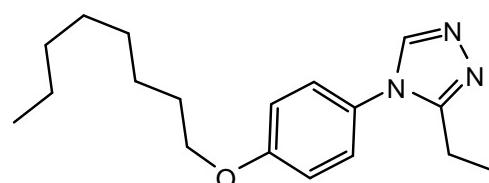
## Compound 47



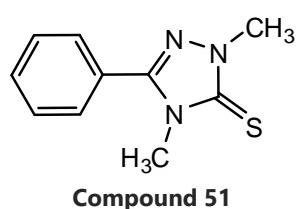
Compound 48



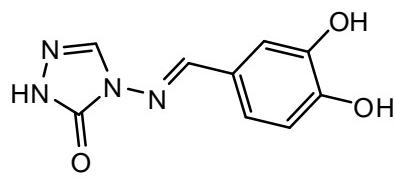
Compound 49



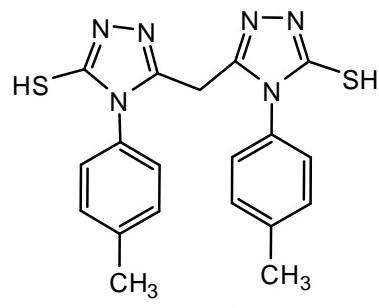
### Compound 50



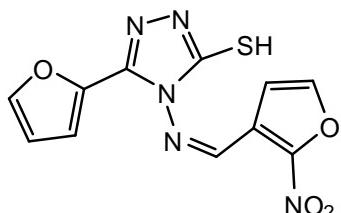
## Compound 51



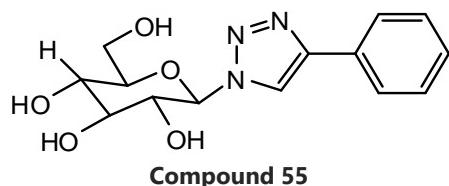
Compound 52



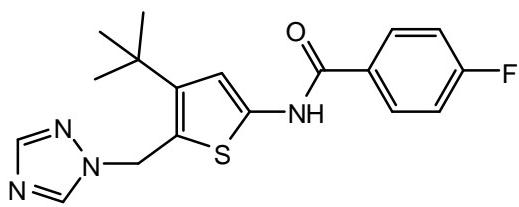
Compound 53



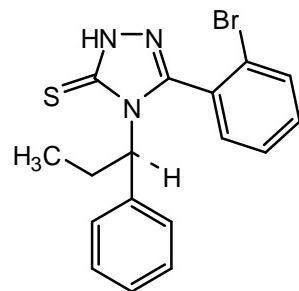
Compound 54



Compound 55



Compound 56



Compound 57

**Funding**

This study has not received any external funding.

**Conflict of Interest**

The authors declare that there are no conflicts of interests.

**Data and materials availability**

All data associated with this study are present in the paper.

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